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(54) Title of the Invention: **Water-Based Bile Acid Agent for Internal Use**

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**Clean Copy of Specification (Contents Unchanged)**

**Specification**

**1. Title of the Invention**

**Water-Based Bile Acid Agent for Internal Use**

**2 Claims**

(1) A water-based bile acid agent for internal use, wherein the compounding weight ratio of dextrin to bile acid is 30:1 or higher and the dextrin concentration is 35% (W/W) or less in a water-based agent containing a bile acid and a dextrin.

(2) The water-based bile acid agent for internal use described in claim 1, wherein the bile acid is ursodeoxycholic acid or chenodeoxycholic acid.

(3) The water-based bile acid agent for internal use described in claim 2, wherein the dextrin is amylopectin, maltodextrin or erythrodextrin.

**3. Detailed Description of the Invention**

**Industrial Field of Application**

[01] The present invention relates to a water-based bile acid agent for internal use containing a bile acid and a dextrin. The water-based bile acid agent for internal use in the present invention is a clear liquid agent in which the bile acid has been solubilized in water. Because this masks the extreme bitter taste of bile acid solids, it can be used as a bile acid medicine administered orally.

### Prior Art

[02] Bile acid is widely used as a cholagogue, a medicine highly valued for its performance and effect. However, bile acid is not very soluble in water and has an extremely bitter taste. Therefore, it has been very difficult to develop a non-bitter bile acid aqueous solution. At the present time, this has hindered the preparation of a water-based agent for internal use that is easier for the digestive tract to absorb than a solid formulation such as a tablet or grains.

[03] Methods of the prior art used to obtain bile acid aqueous solution formulations include solubilizing bile acid in sodium salts (Japanese Examined Patent Application Publication [Kokoku] No. 35-17149) and solubilizing bile acid in clathrate compounds such as  $\beta$ -cyclodextrin (Japanese Unexamined Patent Application Publication [Kokai] No. 55-22616). One method of reducing the bitter taste of bile acid aqueous solutions is to use a sweetener such as sucrose or honey [Basic Course in Drug Development XI: Drug Preparation Methods (Part II), p. 706, Chijinshokan, 15 November 1971].

### Problem Solved by the Invention

[04] However, because the solubility method using bile acid salts requires an aqueous solution value between 9.5 and 100, careful pH control is essential and it is difficult to obtain a water-based agent for internal use that is neutral or weakly acidic. In this method, moreover, the bitter taste in the bile acid aqueous solution is not completely eliminated and is sometimes strong. In the solubility

method using clathrate compounds, because the resulting clathrate compounds are bulky (apparent specific gravity 0.04 g/cc, scattering rate 38-45%) and in the form of a fine powder, they are extremely difficult to handle during preparation of the water-based agent for internal use and the scattering of bile acid may have an adverse effect on the health of workers preparing the formulation. The method of reducing the bitter taste of bile acid by using a sweetener also does not completely mask the bitter taste of bile acid in an aqueous solution and leaves an unpleasant aftertaste during oral administration. The bile acid, moreover, is not completely solubilized in syrup containing sucrose or honey, which is a fatal flaw. The present inventors have conducted extensive research on pharmaceutical additives for solubilizing and dispersing difficult-to-solubilize compounds. For example, they have conducted experimental preparation of bile acid aqueous solutions using macromolecular compounds such as sodium carboxymethylcellulose and hydroxypropylcellulose as well as surfactants such as stearic acid polyoxyl 40 and polyethylene glycol. In all of these tests, the solubility and bitter taste masking were never simultaneously adequate.

#### Means of Solving the Problem

[05] However, when preparing a bile acid aqueous solution using a common dextrin as a binder or formulation diluent, the present inventors surprisingly produced a clear aqueous solution in which the bile acid was completely solubilized and in which there was no bitter taste. The present invention is the product of this discovery.

[06] In other words, the present invention is a water-based bile acid agent for internal use, wherein the compounding weight ratio of dextrin to bile acid is 30:1 or higher and the dextrin concentration is 35% (W/W) or less in a water-based agent containing a bile acid and a dextrin (hereinafter referred to as the water-based agent of the present invention).

[07] The amount of bile acid contained in the water-based agent of the present invention can be anywhere within the range of pharmacological effectiveness for bile acid. The amount of dextrin in the water-based agent of the present invention should have a compounding weight ratio of 30:1 or higher with respect to the bile acid and an overall concentration in the water-based agent of 35% (W/W) or less. If (1) the compounding weight ratio is lower than 30:1, the bile acid does not solubilize sufficiently in the water and a water-based bile acid agent cannot be obtained. Furthermore, the bitter taste of the bile acid is not masked sufficiently. If (2) the dextrin concentration exceeds 35% (W/W), the bile acid does not solubilize adequately and the resulting aqueous solution is cloudy. Because an aqueous solution containing dextrin is essentially weakly acidic, the pH of the resulting water-based agent of the present invention can be adjusted relatively easily to obtain a neutral or weakly acidic water-based agent for internal use.

[08] The bile acids that can be used are ursodeoxycholic acid and chenodeoxycholic acid. The dextrans that can be used are amylopectin, maltodextrin and erythropectin.

[09] The essential ingredients of the water-based agent of the present invention are bile acid, dextrin and water. In addition to these three ingredients, other additives can be included during preparation of the agent. These include binding agents such as hydroxypropylcellulose and polyvinylpyrrolidone, surfactants such as stearic acid polyoxyl 40, polyoxyethylene-hardened castor oil 60 and propylene glycol, and a small amount of ethanol. Other medicinal additives include preservatives to preserve the bile acid, flavorings and sweeteners. If necessary, supplemental preservatives can be added. Examples of preservatives include butyl paraoxybenzoate, propyl paraoxybenzoate or dehydroacetic acid. Examples of sweeteners include sucrose, glucose, sodium citrate and sodium phosphate. Flavorings include menthol, orange flavoring, strawberry flavoring, vanilla flavoring, liquid cinnamon and plum flavoring. Supplemental preservatives include citric acid, hydrochloric acid and phosphoric acid.

[10] Effective ingredients that supplement the bile acid can be added to the water-based agent of the present invention. These include fortifying agents such as  $\gamma$ -orizanol, taurine and royal jelly; vitamins such as thiamine chloride, riboflavin, hydroxine chloride, ascorbic acid, tocopherol, biotin and calcium

pantothenate; and natural medicinals such as gentian, cinnamon, vervain, licorice, ginger, fennel and carrot.

[11] In the water-based agent of the present invention, 1 ppw bile acid and 30 ppw or more dextrin are mixed together in a fluidized bed. While the appropriate amount of binding solution is sprayed on the bed, this mixture is granulated at a circulating warm air temperature of 50-80°C. Water is added, and the grains are stirred and dissolved in the water at a temperature of 15-70°C. The solution can be adjusted at the same temperature using water until the final concentration of dextrin is 35% (W/W) or less. (Hereinafter, this method is referred to as the fluidized-bed granulation method.) An appropriate binding solution is a binding agent such as water or hydroxypropylcellulose and polyvinylpyrrolidone or an aqueous solution or ethanol aqueous solution containing a surfactant such as stearic acid polyoxyl 40, polyoxyethylene-hardened castor oil 60 or polypropylene glycol. In the granulation stage of the fluidized-bed granulation method, the resulting grains have extremely low scattering properties. In other words, the grains obtained in this manner have an apparent specific gravity 0.35-0.61 g/cc and a scattering rate of 8-13%.

[12] Also, after evenly dispersing 1 ppw bile acid in water, 30 ppw or more dextrin can be added to the dispersant, stirred and dissolved at 15-70°C, and adjusted at the same temperature with water so the final concentration of dextrin is 35% (W/W) or less. (This method is hereinafter referred to as the dispersal method.) In the stage of the dispersal method where the bile acid dispersant is

obtained, the bile acid (apparent specific gravity 0.18-0.25 g/cc, scattering rate 15-24%) can be simply added or dissolved in ethanol to improve the dispersion properties before being added. If necessary, a surfactant such as stearic acid polyoxyl 40, polyoxyethylene-hardened castor oil 60 or polypropylene glycol can be added.

[13] Compared to the method of solubilizing bile acid in clathrate compounds (apparent specific gravity 0.04 g/cc, scattering rate 38-44%) (Kokai No. 55-22616), the clear water-based bile acid agents for internal use obtained using the fluidized-bed granulation method and dispersal method pose less risk of scattering bile acid and are easier to handle.

[14] When preservatives, sweeteners, flavorings, supplemental preservatives and other additives are used in the water-based agent of the present invention, they are added in the granulation stage of the fluidized-bed granulation method and in the stage where the bile acid dispersant is obtained in the dispersal method. However, the medicinal additives can be added in the bile acid solubilizing stage of both methods after the bile acid has been stirred and dissolved. If other active ingredients are to be included in the water-based agent of the present invention in addition to bile acid, they too should be added in the bile acid solubilizing stage of both methods. These active ingredients can be added alone or in an aqueous solution or aqueous suspension of vitamins and



nutrients. These can include natural medicinals such as plant extracts, liquid plant extracts, and plant tinctures.

#### **Operation and Effect of the Invention**

[15] The following is an explanation of the bile acid solubilizing effect and bitter taste masking effect of dextrin in the water-based agent of the present invention.

[16] In a test of bile acid solubilizing effects and bitter taste masking effects, 70 different samples were prepared and used. In this test, varying amounts of ursodeoxycholic acid (apparent specific gravity 0.24 g/cc, scattering rate 17%) or chenodeoxycholic acid (apparent specific gravity 0.19 g/cc, scattering rate 22%) were dispersed evenly in distilled water, varying amounts of amylopectin, erythropectin or maltodextrin were added, the solution was stirred and mixed at 20-65°C, and the sample was adjusted with water at the same temperature to a total weight of 100 g. The various components in these samples except for the water are shown in the water-based agent composition lines of Table 1 and Table 2. These samples were adjusted so that the pH was between 3.3 and 5.0, that is, weakly acidic.

[17] The bile acid solubilizing effect was determined by measuring the light absorptivity of the samples at 660 nm using a spectrophotometer and by examining the samples with the naked eye to see if they were clear. The bitter taste masking effect was determined in a bitterness taste test with 10 panellists.

[18] The results from the bile acid solubilizing test and bitter taste masking test are shown in Table 1 and Table 2. In the clearness test using the naked eye, + means cloudy,  $\pm$  means somewhat cloudy, and - means clear. In the bitter taste-masking test, the panelists placed 10 g of each sample in their mouths for 20 seconds to determine if they could taste any bitterness. Here, 0 means all ten panelists perceived no bitterness,  $\Delta$  means 1 to 7 panelists perceived some bitterness, and x means 8 or more panelists perceived some bitterness. In both tests, the ratio of dextrin to bile acid in the samples was the significant factor.

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FIG 1

Sample No.	1	2	3	4	5	6	7	8	9	10
Agent Composition										
Unsedoxycetic Acid (mg)	12	30	120	200	240	120	200	240	12	25
Amylodextrin (g)	6	6	6	6	6	6	6	6	15	15
Maltodextrin (g)	6	6	6	6	6	6	6	6	6	6
Dextrin Concentration % (W/W)	500	200	50	30	25	50	30	25	150	15
Compounding Ratio	0.008	0.008	0.012	0.058	0.302	0.050	0.089	0.492	0.006	0.008
Light Absorbivity	0	0	0	0	+	0	0	+	0	0
Clarity	0	0	0	0	+	0	0	+	0	0
Bitterness Masking Effect	0	0	0	0	+	0	0	+	0	0

FIG 1 (Continued)

Sample No.	11	12	13	14	15	16	17	18	19	20
Agent Composition										
Unsedoxycetic Acid (mg)	250	500	600	250	500	600	50	100	600	1000
Amylodextrin (g)	15	15	15	15	15	15	30	30	30	30
Maltodextrin (g)	15	15	15	15	15	15	30	30	30	30
Dextrin Concentration % (W/W)	60	30	25	60	30	25	500	300	50	30
Compounding Ratio	0.032	0.084	0.00	0.048	0.092	0.78	0.008	0.010	0.080	0.084
Light Absorbivity	0	0	+	0	0	+	0	0	0	0
Clarity	0	0	+	0	0	+	0	0	0	0
Bitterness Masking Effect	0	0	+	0	0	+	0	0	0	0

FIG 1 (Continued)

Sample No.	21	22	23	24	25	26	27	28	29	30
Agent Composition										
Unsedoxycetic Acid (mg)	1200	600	1000	1200	70	233	437	1167	1750	437
Amylodextrin (g)	30	30	30	30	35	35	35	35	35	35
Maltodextrin (g)	30	30	30	30	35	35	35	35	35	35
Dextrin Concentration % (W/W)	30	30	30	30	35	35	35	35	35	35
Compounding Ratio	25	50	30	25	600	160	60	30	20	80
Light Absorbivity	0.89	0.080	0.102	0.98	0.022	0.074	0.088	0.101	1.1	0.100
Clarity	+	0	0	+	0	0	0	0	+	0
Bitterness Masking Effect	+	0	0	+	0	0	0	0	+	0

FIG 1 (Continued)

Sample No.	31	32	33	34	35	36	37	38	39	40
Agent Composition										
Chondrooxycholic Acid (mg)	1187	1750	80	200	400	500	800	80	200	400
Amlyodextrin (g)			40	40	40	40	40			
Melodextrin (g)	35	35						40	40	40
Dextrin Concentration % (W/W)			40	40	40	40	40	40	40	40
Compounding Ratio	32	20	500	200	100	80	50	500	200	100
Light Absorptivity	0.102	1.3	0.284	0.62	0.98	1.4	1.5	0.428	0.84	0.98
Clarity				+	+	+	+	+	+	+
Bitterness Masking Effect	O	A	O	A	A	x	x	O	A	x

FIG 2

Sample No.	41	42	43	44	45	46	47	48	49	50
Agent Composition										
Chondrooxycholic Acid (mg)	25	100	250	333	400	250	333	400	60	100
Amlyodextrin (g)	10	10	10	10	10				30	30
Erythroclatrin (g)						10	10	10		
Dextrin Concentration % (W/W)	10	10	10	10	10	10	10	10	30	30
Compounding Ratio	400	100	40	30	25	40	30	25	500	300
Light Absorptivity	0.008	0.008	0.022	0.070	0.505	0.040	0.088	0.668	0.010	0.022
Clarity					+			+		
Bitterness Masking Effect	O	O	O	O	A	O	O	A	O	O

FIG 2 (Continued)

Sample No.	51	52	53	54	55	56	57	58	59	60
Agent Composition										
Chondrooxycholic Acid (mg)	800	100	1200	1000	1200	70	233	437	1167	1750
Amlyodextrin (g)	30	30	30			35	35	35	35	35
Erythroclatrin (g)				30	30					
Dextrin Concentration % (W/W)	30	30	30	30	30	35	35	35	35	35
Compounding Ratio	50	30	25	30	25	600	150	80	30	20
Light Absorptivity	0.084	0.100	0.92	0.098	1.1	0.009	0.048	0.100	0.102	1.2
Clarity			+		+					+
Bitterness Masking Effect	O	O	A	O	A	O	O	O	O	x

FIG 2 (Continued)

Sample No.	61	62	63	64	65	66	67	68	69	70
Agent Composition										
Chenodeoxycholic Acid (mg)	1187	1760	80	200	400	500	800	80	200	400
Amniotexin (g)			40	40	40	40	40			
Erythrodextrin (g)	35	35						40	40	40
Dextrin Concentration % (W/W)	35	35	40	40	40	40	40	40	40	40
Compounding Ratio	30	20	500	200	100	80	50	500	200	100
Light Absorptivity	0.104	1.4	0.338	0.74	0.98	1.3	1.8	0.58	0.80	1.2
Clarity	-	+	±	+	+	+	+	+	+	+
Diffract Masking Effect	O	x	O	A	x	x	x	O	A	x

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[19] As can be seen in Table 1 and Table 2, the water-based bile acid agents for internal use in which the compounding weight ratio of dextrin to bile acid is 30:1 or higher and in which the dextrin concentration is 35% (W/W) or less are clear aqueous solutions in which the bile acid has been solubilized in the water to a remarkable degree, in which the light absorptivity is less than 0.1, and in which the bitter taste of the bile acid solids has been sufficiently masked. As a result, the water-based bile acid agents of the present invention can be used as non-bitter water-based agents for internal use.

[20] Most of the samples described above correspond to working examples of the present invention. However, in order to explain the present invention further, the following is a description of additional working examples.

#### Working Example 1

[21] First, 10 g of ursodeoxycholic acid and 1 g of butyl paraoxybenzoate were solubilized in ethanol to obtain exactly 100 ml of solution. Next, 1 ml of the ethanol solution was measured out using a measuring pipette, introduced to 80 g of sterilized water, and dispersed evenly. Next, 3 g of amylopectin was added to the dispersant and then stirred and mixed evenly at a temperature of 60-65°C. When the amylopectin was added, the cloudy dispersant immediately became clear and the bitter taste was completely imperceptible.

[22] Next, to the aqueous solution were added 350 mg of licorice extract, 0.8 ml of liquid ginger extract, 1.5 ml of fennel extract, 0.5 ml of liquid cinnamon

extract, 130 mg of carrot extract, 0.1 ml of plum flavoring, 10 g of glucose, and 0.5 g of polyoxyethylene-hardened castor oil 60. The contents were stirred and mixed thoroughly, the solution was passed through a 0.45  $\mu$  membrane filter for sterilization filtration, and sterilized water was added to the filtered solution until the total amount was 100 g. The resulting solution was divided evenly in five 20 ml drink containers, which were then sealed with metal caps to obtain an orally administered gastrointestinal agent. When the amount of ursodeoxycholic acid in each container was measured using gas chromatography, the results were  $19.8 \pm 0.3$  mg.

#### Working Example 2

[23] First, 5 g of chenodeoxycholic acid (apparent specific gravity 0.18 g/cc, scattering rate 24%) and 490 g maltodextrin were measured out and added to a Freund FLO-1 fluidized-bed granulator for mixing. While spraying 100 g of a 40% (W/W) aqueous ethanol solution containing 1% (W/W) hydroxypropylcellulose into the fluidized bed, fluidized-bed granulation was performed at a circulating warm air temperature of 60°C and the resulting grains were sized to 32 mesh. The resulting grains had an apparent specific gravity of 0.41 g/cc and a scattering rate of 10%.

[24] When 32 g of the grains were added to 80 g of sterilized water and mixed in thoroughly, the resulting clear aqueous solution had no bitter taste and was somewhat sweet tasting. Next, 1 ml of an ethanol aqueous solution containing 1% (W/V) butyl paraoxybenzoate and 0.5 g of stearic acid polyoxyl 40 were added to the aqueous solution, stirred and mixed thoroughly, and added to

sterilized water to reach a total weight of 120 g. The resulting solution was divided evenly in four 30 ml drink containers, which were then sealed with metal caps to obtain an orally administered agent. When the amount of chenodeoxycholic acid in each container was measured using gas chromatography, the results were  $79.5 \pm 0.8$  mg.

### Working Example 3

[25] First, 5 g of ursodeoxycholic acid (apparent specific gravity 0.25 g/cc, scattering rate 15%) and 395 g erythrodextrin were measured out and added to a Freund FLO-1 fluidized-bed granulator for mixing. While spraying 80 g of water into the fluidized bed, fluidized-bed granulation was performed at a circulating warm air temperature of 60°C and the resulting grains were sized to 32 mesh. The resulting grains had an apparent specific gravity of 0.57 g/cc and a scattering rate of 9%.

[26] When 4 g of these grains were added to 70 g of sterilized water and stirred in thoroughly, a clear aqueous solution was obtained with no bitter taste at all.

[27] Next, to the aqueous solution were added 20 mg of thiamine chloride, 10 mg of tocopherol acetate, 5 mg of riboflavin phosphate, 50 µg of biotin, 1000 mg of taurine, 250 mg of royal jelly, 15 g of sucrose, 0.1 ml of propylene glycol, and 0.1 ml of orange flavoring. After thorough mixing, the solution was adjusted with sterilized water to a total weight of 100 g. The contents were stirred and mixed



thoroughly and the solution was then passed through a 0.45  $\mu$  membrane filter for sterilization filtration. The resulting solution was divided evenly in five 20 ml drink containers, which were then sealed with metal caps to obtain an orally administered nutrient enriched agent. When the amount of ursodeoxycholic acid in each container was measured using gas chromatography, the results were 9.9  $\pm$  0.2 mg.

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Amendment of Proceedings (Filed by Applicant)

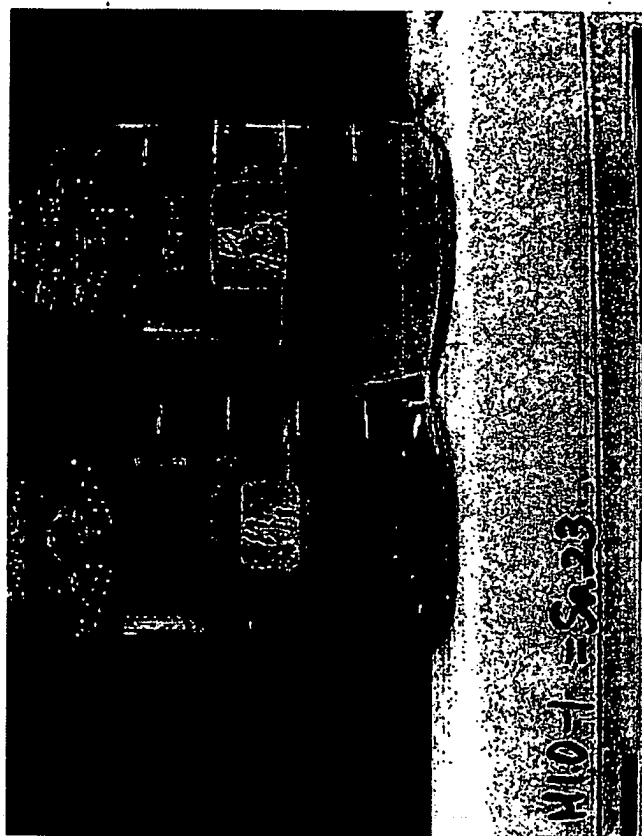
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To the Honorable Michio UGA, Director-General of the Japanese Patent Office

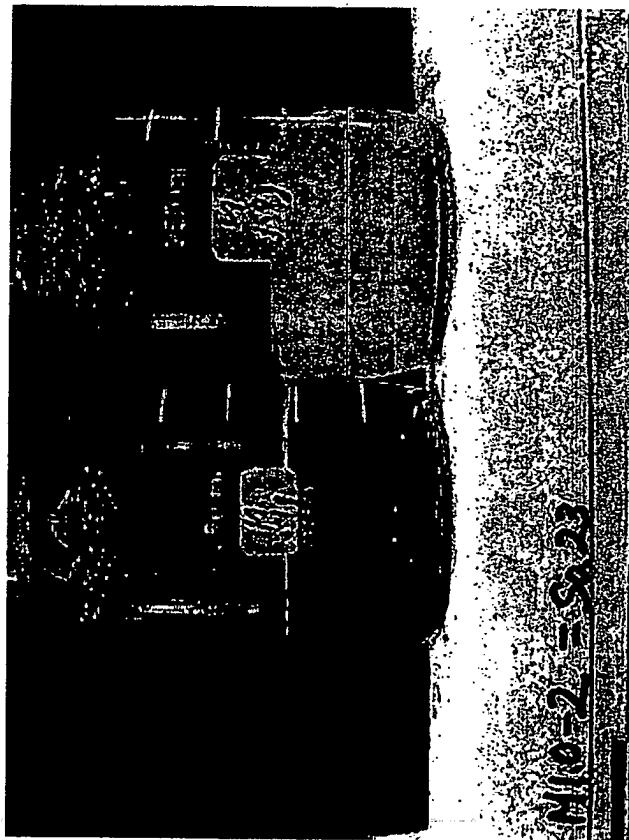
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      Patent Application No. 60-292933
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3.    Party Filing the Amendment  
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6.    Section to be Amended    Entire Specification
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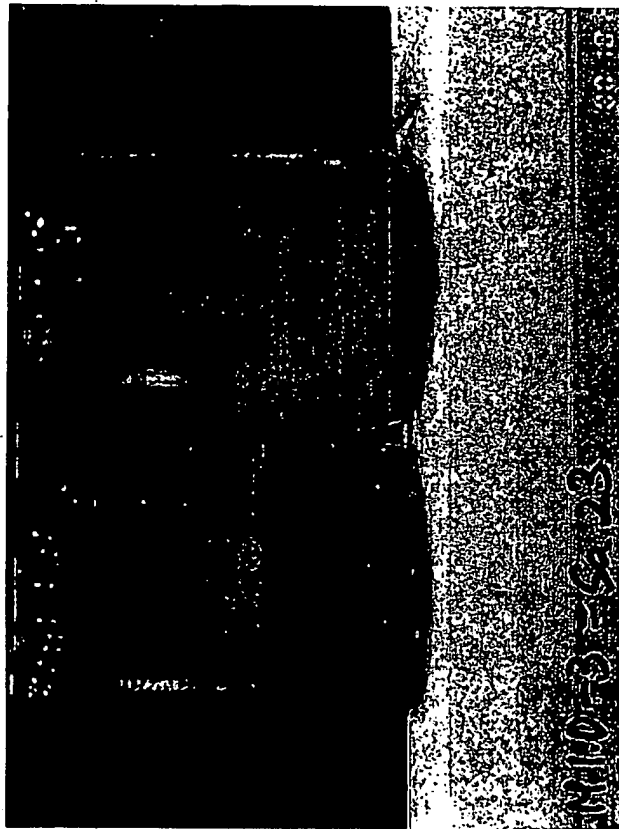
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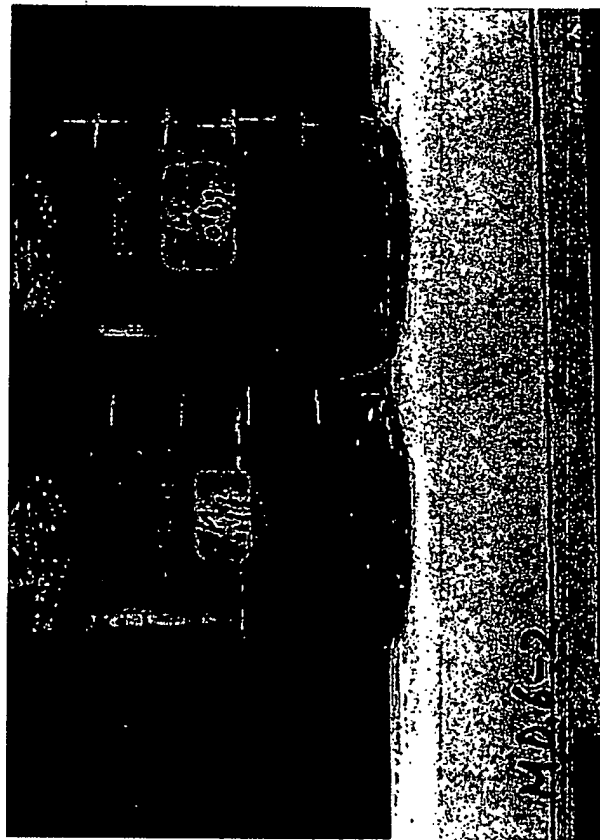


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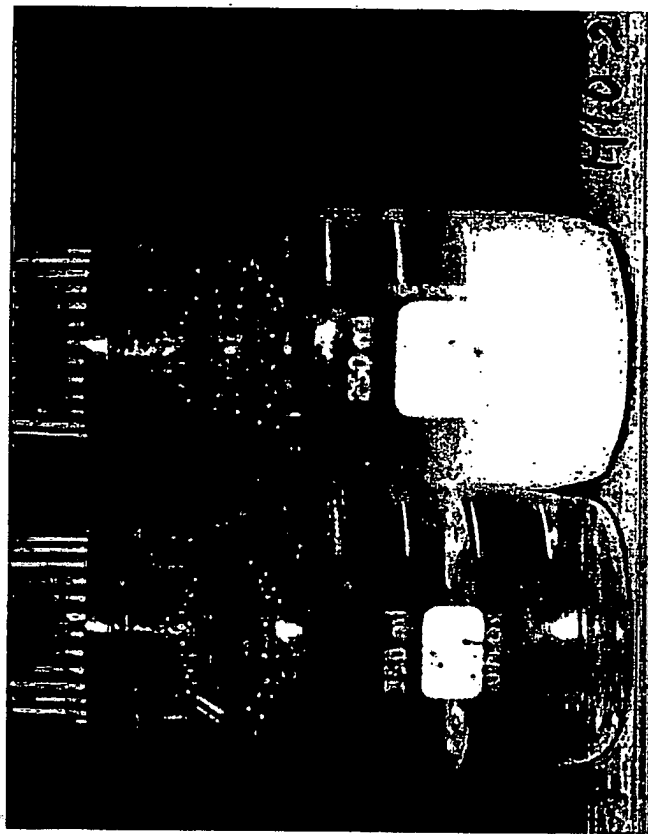
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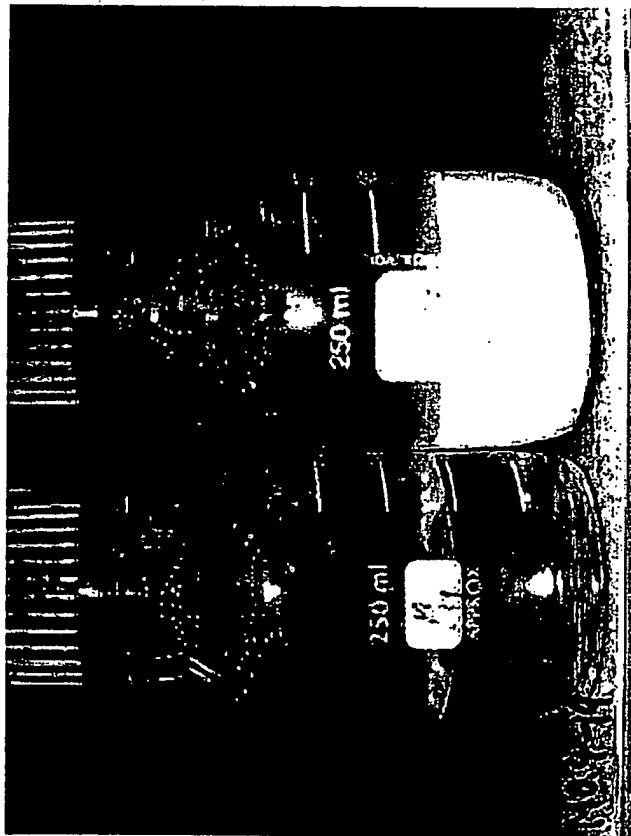
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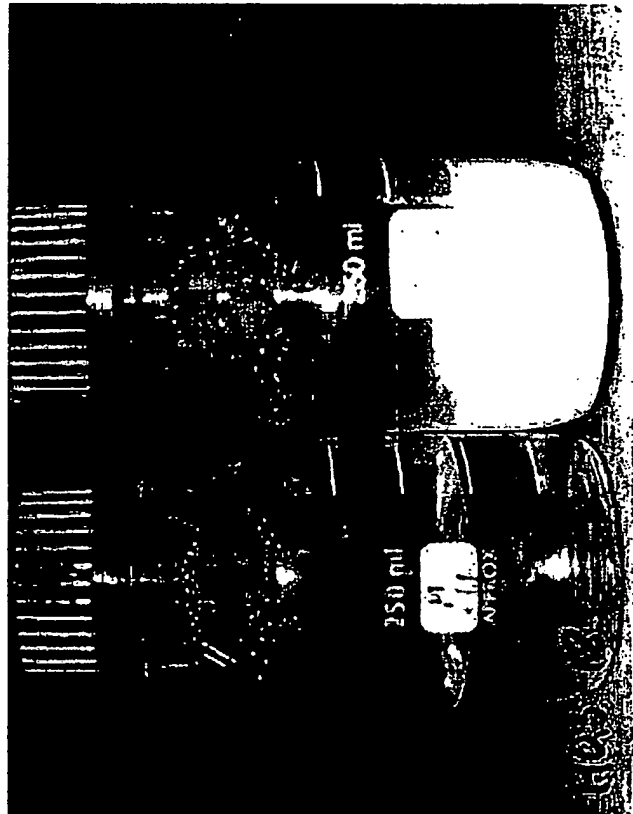
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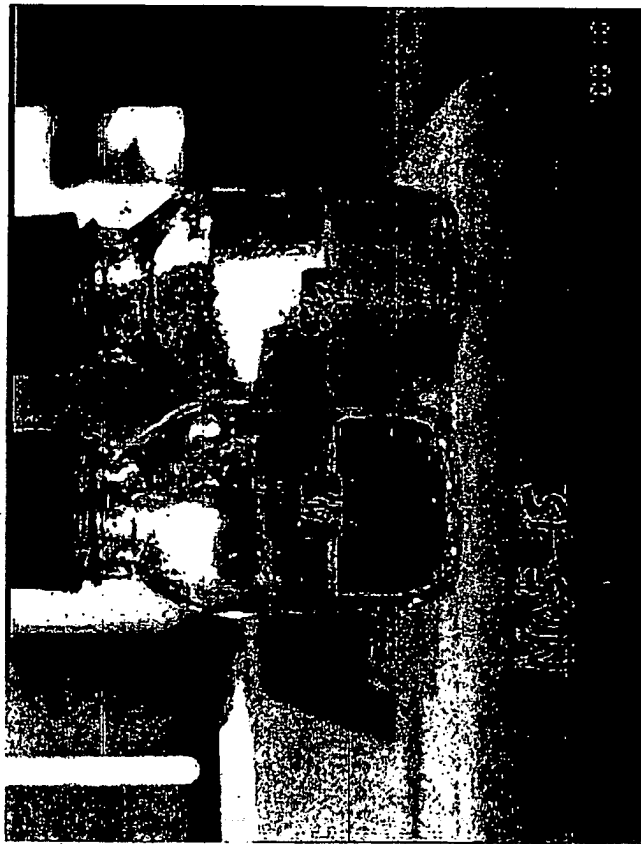
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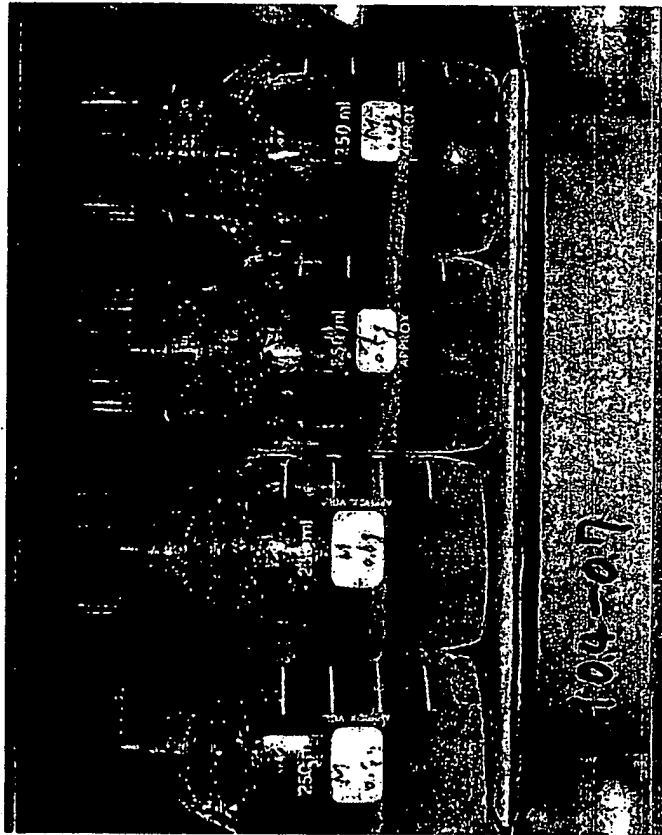
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